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Choroidal Proteins Involved in Cerebrospinal Fluid Production may be Potential Drug Targets for Alzheimer's Disease Therapy

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Abstract: Alzheimer's disease is known to be the most common form of dementia in the elderly. It is clinically characterized by impairment of cognitive functions, as well as changes in personality, behavioral disturbances and an impaired ability to perform activities of daily living. To date, there are no effective ways to cure or reverse the disease. Genetic studies of early-onset familial Alzheimer's disease cases revealed causative mutations in the genes encoding β -amyloid precursor protein and the γ -secretase-complex components presenilin-1 and presenilin-2, supporting an important role of β -amyloid in the pathogenesis of Alzheimer's disease. Compromised function of the choroid plexus and defective cerebrospinal fluid production and turnover, with diminished clearance of β -amyloid, may play an important role in late-onset forms of Alzheimer's disease. If reduced cerebrospinal fluid turnover is a risk factor for Alzheimer's disease, then therapeutic strategies to improve cerebrospinal fluid flow are reasonable. However, the role of deficient cerebrospinal fluid dynamics in Alzheimer's disease and the relevance of choroidal proteins as potential therapeutic targets to enhance cerebrospinal fluid turnover have received relatively little research attention. In this paper, we discuss several choroidal proteins, such as $\text{Na}^+\text{-K}^+$ ATPase, carbonic anhydrase, and aquaporin 1, that may be targets for pharmacological up-regulation of cerebrospinal fluid formation. The search for potentially beneficial drugs useful to ameliorate Alzheimer's disease by facilitating cerebrospinal fluid production and turnover may be an important area for future research. However, the ultimate utility of such modulators in the management of Alzheimer's disease remains to be determined. Here, we hypothesize that caffeine, the most commonly used psychoactive drug in the world, may be an attractive therapeutic candidate for treatment of Alzheimer's disease since long-term caffeine consumption may augment cerebrospinal fluid production. Other potential mechanisms of cognitive protection by caffeine have been suggested by recent studies.

Keywords: Alzheimer's disease, aquaporin 1, caffeine, carbonic anhydrase II, cerebrospinal fluid pressure, cerebrospinal fluid production, choroid plexus, intracranial pressure, $\text{Na}^+\text{-K}^+$ ATPase, SLC4A10

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Introduction

Alzheimer's disease (AD), the most common type of dementia among older people, is a progressive neurodegenerative disorder characterized clinically by a gradual decline in cognition and daily functioning and behavioural alterations.¹ Principal neuropathological hallmarks of AD include extracellular senile plaques containing β -amyloid ($A\beta$) derived from β -amyloid precursor protein (APP) after sequential cleavage by β -secretase and γ -secretase, and intracellular neurofibrillary tangles caused by abnormally phosphorylated tau protein.¹ Despite major advances in understanding the molecular etiology of the disease, progress in the clinical treatment of AD patients has been extremely limited. Therefore, new and more effective therapeutic approaches are needed. Early-onset familial AD caused by mutations in the genes encoding APP and the γ -secretase-complex components presenilin-1 and presenilin-2 accounts for less than 5% of the total number of AD cases.² The discovery of pathogenic mutations in these three genes in rare patients with autosomal dominant, early-onset AD provided incontestable evidence that aberrant APP processing can be sufficient to trigger the pathological cascade leading to AD.³ The pathological accumulation of $A\beta$ in the far more common late-onset AD is more likely to be the result of defects in the clearance of $A\beta$.³ There is evidence that production and turnover of cerebrospinal fluid (CSF) help to clear toxic molecules such as $A\beta$ from the interstitial-fluid space of the brain to the bloodstream.⁴ Reduced formation of CSF, with diminished clearance of β -amyloid, is suspected to be a contributor to the pathogenesis of AD.⁴ Consequently, pharmacological targeting of choroidal proteins involved in CSF production may provide a new therapeutic approach for AD since such modulators may improve the CSF turnover and clearance of potentially toxic metabolites, such as $A\beta$, from the brain. However, the role of deficient CSF dynamics in AD and the relevance of choroidal proteins as potential therapeutic targets to enhance CSF turnover have received relatively little research attention. In this paper, we discuss several choroidal proteins that may be targets for pharmacological up-regulation of CSF formation, and hypothesize that caffeine may be an attractive therapeutic candidate for treatment of AD since long-term caffeine consumption may augment CSF production.

Abnormal CSF Flow may be Linked to AD

CSF production and turnover have been shown to be decreased in aging and in pathological conditions, such as normal pressure hydrocephalus (NPH) and AD.⁴ In NPH, there is evidence for CSF stagnation with decreased clearance of various macromolecules.⁵ Although the primary change in NPH is an increase in CSF outflow resistance, decreased CSF production also has been reported.^{4–6} Both conditions lead to a decrease in CSF turnover and, in turn, a decreased clearance of macromolecules.⁵ In NPH, a decrease in clearance of $A\beta$ and tau is suggested by the higher than expected coincidence of AD pathology in cortical biopsy samples obtained at shunt implantation.⁵ The coincidence of AD neuropathology among patients with NPH varies from 25%–75% depending upon the severity of the clinical dementia.⁷ As noted above, a decrease in CSF production is also found in AD.⁸ Using the Masserman technique, Silverberg et al⁸ measured a 50% decrease in CSF production among AD patients when compared with Parkinson's disease controls. Mean CSF production in AD was 0.20 ± 0.06 ml/min, and in controls was 0.42 ± 0.13 ml/min.⁴ The authors calculated a three-fold decrease in CSF turnover in AD.⁴ Age-associated reduction in CSF production, with diminished clearance of $A\beta$, may be a key factor in the onset and progression of AD,⁴ and may be a particularly important mechanism of amyloid toxicity in late-onset AD cases in whom overproduction of $A\beta$ may not be operative. Higher concentrations of $A\beta$ increase the probability of aggregation and fibril formation.^{4,9} Hence, reduced CSF clearance of $A\beta$ should facilitate amyloid burden in the brain.⁴ In contrast to the 40-amino acid form of $A\beta$, the longer 42-residue form is more prone to aggregate and form plaques.⁴

Data on the relationship between AD and cerebrospinal fluid pressure (CSFP) are rather scarce in the literature. Intracranial pressure (ICP) depends on cerebral tissue volume, cerebrospinal fluid volume and cerebral blood volume. Interestingly, Silverberg et al⁷ reported in 2006 on intraventricular CSFP in patients with AD. Seven of the 181 subjects (3.9%) with no clinical or radiographic signs of NPH had an opening CSFP >200 mmH₂O.⁷ For this AD-elevated CSFP group, the mean CSFP was 249 ± 20 mmH₂O. As the authors hypothesised previously, in the setting

of pre-existing AD, NPH could arise with an increase in CSF outflow resistance due to amyloid deposition and fibrosis in the meninges and arachnoid granulations.⁷ In an animal model of NPH, CSFP is initially elevated but soon returns to normal after ventricular enlargement, decreased CSF production and other compensatory events.^{7,10} Silverberg et al⁷ anticipated that the AD patients in their study with elevated CSFP were in the earliest stages of this process at the time that their elevated pressures were discovered, and that over time they would go on to develop enlarged ventricles and clinical signs of NPH. The AD group without elevated CSFP consisted of 174 subjects (the remaining 96.1%). Mean opening CSFP in this group was 103 ± 47 mm H₂O, which was statistically significantly lower when compared to the AD-elevated CSFP group and a somewhat younger non-demented control group of subjects with Parkinson's disease (140 ± 60 mm H₂O).^{6,7} Forty-two of the 174 subjects (24.1%) had a CSFP lower than the normal range.¹¹ This is a much higher proportion than one would expect from a normal population. An unexpected finding of this study was the relatively high (>30%) proportion of subjects with moderate to severe dementia as measured by Mattis Dementia Rating Scale total scores below 100, despite inclusion-exclusion criteria designed to capture subjects with mild to moderate dementia (Mini-Mental State Examination score between 15 and 24, inclusive).^{7,12} Although not specifically investigated in this study, cerebral atrophy associated with moderate to severe AD could be hypothesised to be associated with lower CSFP.¹¹ Theoretically, the marked reduction in CSF production observed in AD patients might lead to a further reduction of the CSFP.

There is some scientific rationale for considering AD, at least in part, to be a choroid plexus (CP) disease, in that reduced CSF production and turnover may contribute to the difficulty in clearing A β from the aging brain.¹³ CSF is produced mainly by the four choroid plexuses that are found one in each ventricle of the brain.^{1,4,13-16} The CPs are highly vascularized villous structures covered by a single layer of epithelial cells.^{15,16} CPs have multiple functions of synthesis, secretion, active transport and selective reabsorption of deleterious substances.¹⁵ In young adults, CSF is completely renewed six times a day.¹³ Choroid

epithelial cells synthesize numerous crucial molecules, such as transthyretin, which sequesters the β -amyloid protein and inhibits fibrillogenesis.^{13,16} The levels of transthyretin have been reported to be lowered in the CSF of AD patients.¹⁵ Structural changes in the CP coincide with diminished CSF production in ageing, AD, and NPH.⁴ In AD, choroid plexuses present similar, although much more pronounced, abnormalities than those observed in ageing.^{15,16} The CP in AD shows epithelial atrophy, basement membrane thickening, cyst formation, lipid accumulation, fibrosis, calcification, and hyalinisation and amyloid deposition in choroidal blood vessels.⁴

Mechanisms of CSF Formation

A review by Brown et al¹⁴ highlighted the molecular mechanisms of CSF production. The epithelial cells of the CP secrete CSF, by a process that involves the transport of Na⁺, Cl⁻ and HCO₃⁻ from the blood to the ventricles of the brain.¹⁴ This creates an osmotic gradient that is accompanied by the secretion of H₂O.¹⁴ The movement of ions across the cellular membrane is mediated by specific transporters and ion channels that are distributed unequally on the basolateral and apical sides of the CP epithelial layer.¹⁴ Na⁺-K⁺ ATPase, K⁺ channels and Na⁺-K⁺-2Cl⁻ cotransporters are expressed in the apical membrane.¹⁴ By contrast the basolateral membrane contains Cl⁻-HCO₃⁻ exchangers, a variety of Na⁺-coupled HCO₃⁻ transporters and K⁺-Cl⁻ cotransporters.¹⁴ Aquaporin 1 (AQP1) mediates water transport at the apical membrane, but the route across the basolateral membrane is unknown.¹⁴

Although stasis of CSF may be a factor in the etiology of AD, potential pharmacological strategies to improve CSF flow have received little research attention. Possible approaches to modify CSF formation were elaborated in a review by Johanson et al.¹⁷ However, this field remains largely unexplored in AD. In the present paper, we discuss several possible targets in choroid plexus for pharmacologically augmenting the rate of CSF formation, thereby enhancing CSF turnover that is severely compromised in AD. It is not the purpose of this review to be exhaustive or to discuss all the potential sites for drug actions to accelerate CSF production. Theoretically, transcription factors in the nucleus, enzymes in the cytoplasm, and transporters/channels and receptors at the limiting plasma membrane are all potential drug targets.¹⁷ Instead, the



present review will summarize some relevant data in support of its main view.

Choroidal Proteins Involved In CSF Production as Potential Drug Targets for AD Therapy

Among the numerous proteins involved in choroidal CSF production, it is known that Na⁺-K⁺ ATPase, carbonic anhydrase II (CA II), AQP1, and solute carrier family 4, sodium bicarbonate transporter, member 10 (SLC4A10) are major contributors to CSF secretion.^{18,19} The Na⁺-K⁺ ATPase is a ubiquitous protein which catalyses 1 molecule of ATP to exchange 3 Na⁺ ions for 2 K⁺ ions across the cell membrane.²⁰ In the choroid plexus, this enzyme is located in the luminal surface and provides the driving force for CSF production.¹⁸ Inhibitors of the Na⁺-K⁺ ATPase pump, eg, the cardiac glycoside ouabain, have been shown to reduce CSF production, and the movement of Na⁺ into the CSF.¹⁷ A recent study in rats showed that the long-term consumption of caffeine, the most commonly used psychoactive drug in the world and non-selective adenosine A₁ and A_{2A} receptor antagonist, increased CSF production, associated with the increased expression of Na⁺-K⁺ ATPase and increased cerebral blood flow.¹⁸ By contrast, acute treatment with caffeine decreased the production of CSF, suggesting 'effect inversion' associated with caffeine, which was mediated by increased expression of the A₁ adenosine receptor, in the choroid plexus of rats chronically treated with caffeine.¹⁸ In accordance with previous results showing increased expression of Na⁺-K⁺ ATPase in A₁ adenosine receptor transgenic mice, this study showed that the A₁ adenosine receptor regulates the expression of Na⁺-K⁺ ATPase in the choroid plexus.¹⁸ Because caffeine is commonly ingested chronically, it is important to note that long-term exposure to adenosine receptor antagonists like caffeine can have effects that resemble the acute effects of adenosine receptor agonists, due likely to up-regulation of adenosine receptors (A₁ and A_{2A}) and adaptive changes leading to adenosine receptor sensitization.²¹ Of major interest for the view presented here, recent epidemiological and experimental studies suggest that long-term caffeine consumption may be protective against AD.^{21–23} Epidemiologically, a retrospective study showed that the incidence of AD was

inversely associated with the caffeine intake during the 20 years that preceded diagnosis of AD.²³ Since increased CSF production may improve the CSF turnover and clearance of potentially toxic metabolites, such as Aβ, it seems reasonable to speculate that long-term caffeine consumption could exert protective effects against AD, at least in part by facilitating CSF secretion. To the best of our knowledge, no previous study has suggested increased CSF production as a possible mechanism underlying the inverse association between caffeine consumption and AD. However, there could be other potential mechanisms of cognitive protection by caffeine. Among them, the antioxidant properties of caffeine, its anti-inflammatory capacities, its ability to block disruptions of the blood-brain barrier, and its well-documented blockade of adenosine A₁ and A_{2A} receptors have been proposed to underlie its ability to protect against AD.^{22,24} Furthermore, in a recent study, Arendash et al²² reported that long-term caffeine administration that began in young adulthood protected AD transgenic mice against otherwise certain cognitive impairment in older age, while also limiting their brain production of Aβ due to reduced expression of both β-secretase and presenilin-1/γ-secretase. The ability of caffeine to reduce Aβ production was confirmed in neuronal cell cultures from these same transgenic mice, wherein concentration-dependent decreases in both Aβ (1–40) and Aβ (1–42) were observed.²² In another study, Arendash et al²⁵ found that aged, cognitively-impaired AD transgenic mice given a moderate amount of daily caffeine exhibited a restoration of working memory to the level of normal, aged mice. In these same aged AD mice, which had pre-existing and substantial Aβ burden, caffeine treatment reduced both soluble and deposited (insoluble) brain Aβ levels.²⁵ Cao et al²⁴ recently reported that acute caffeine administration to both young adult and aged AD transgenic mice rapidly reduced Aβ levels in both brain interstitial-fluid and plasma without affecting Aβ elimination. A single treatment with caffeine did not affect the half-life of interstitial-fluid Aβ, demonstrating that caffeine had affected brain Aβ production rather than its elimination.²⁴ The latter, however, is not inconsistent with the idea that long-term caffeine consumption may exert protective effects against AD at least in part by increasing CSF production and clearance.

Indeed, chronic but not acute treatment of rats with caffeine increased CSF production.¹⁸

Carbonic anhydrase, a zinc-containing enzyme, is present in many tissues of the body, including the brain, and catalyzes the interconversion between CO_2 and HCO_3^- .²⁶ There are at least seven isozymes of carbonic anhydrase in humans.²⁶ The most active is isozyme II.²⁶ In addition to its involvement in pH regulation, HCO_3^- reabsorption and CO_2 expiration, CA plays a crucial role in signal processing, long-term synaptic transformation and attentional gating of memory storage.²⁷ Carbonic anhydrases also play an important role in CSF production.^{14,18} The main evidence for this is that acetazolamide, a CA inhibitor, reduces CSF secretion in rats by as much as 50%, and that acetazolamide can also reduce CSF pressure in children with hydrocephalus.¹⁴ CA dysfunction impairs cognition and is associated with mental retardation, Alzheimer's disease and aging.²⁷ A previous study reported significantly lower enzyme activity of carbonic anhydrase in AD autopsy homogenates of the temporal lobe compared with age-matched controls, a fact strongly supporting the involvement of CAs in cognitive dysfunctions characteristic of this disease.^{28,29} Moreover, a study by Masseguin et al³⁰ showed that aging affects choroidal proteins involved in CSF production. The authors compared choroid plexuses of Sprague-Dawley rats aged 10 or 20 months with those of 3-month-old ones.³⁰ Progressive and age-related changes in the $\text{Na}^+\text{-K}^+$ ATPase, carbonic anhydrase II and AQP1 expressions at the apical and/or cytoplasmic level, as suggested by both the decreases in the intensities of immunocytochemical and in situ hybridization signals, indicated that aging decreases notably the protein expression of the enzymes and transporters known to regulate the CSF production in choroid plexus.³⁰ A previous study reported that phenylalanine, a carbonic anhydrase activator, when administered to experimental animals produces a relevant pharmacological enhancement of synaptic efficacy, spatial learning and memory, due to the rapid and efficient increase of bicarbonate concentration in memory-related neural structures.^{29,31,32} This class of enzyme modulators might thus be useful for the treatment of AD, aging and other conditions in which spatial learning and memory therapy need to be enhanced.^{29,31} Interestingly, the well known selective serotonin reuptake inhibitors fluoxetine, sertraline

and citalopram were shown to be very effective in patients with AD who also have major depression.²⁹ Casini et al²⁹ reported the potent activatory properties of these three pharmacological agents against the most widespread isozymes, CA I and CA II, both of which are associated with critical physiological functions in a multitude of tissue. This suggested that the efficacy of these three pharmacological agents in patients with AD who also have major depression might be due, at least in part, to their CA activating properties.²⁹ Given that CAs also play an important role in CSF production, here, we raise the question of whether CA activators could also ameliorate AD by facilitating CSF production, turnover and clearance. However, we are not aware of studies which have investigated this hypothesis.

Other proteins including AQP1 and SLC4A10 are also major contributors to CSF production.^{18,19} SLC4A10 is present in multiple tissues and is expressed in the basolateral membrane of the CP epithelium.^{14,33} This transporter mediates the efflux of one Cl^- in exchange for the influx of one Na^+ and two HCO_3^- .¹⁴ Targeted mutations, such as an exon deletion in SLC4A10 knockout mice, resulted in an 88% reduction in brain ventricle size from decreased CSF production as compared to wild-type mice.^{19,34} The AQP1 water channel mediates water movement across membranes in the brain, kidney, vascular system, and other tissues.³⁵ AQP1 is abundant in the choroid plexus and is likely to have a major role in mediating water transport across the apical membrane during CSF secretion.^{14,35} AQP1 knockout mice showed reduced CSF production and ICP compared with wild-type mice.³⁶ As noted above, aged Sprague-Dawley rats have substantially less AQP1 expression in choroid plexus epithelium than do young ones.³⁰ As noted earlier, with age, CSF production decreases and could increase the risk for development of late-onset AD.⁴ Recently, Johanson et al¹⁷ suggested the possibility of therapeutically up-regulating or restoring AQP1 expression in aged humans when the CSF turnover rate is compromised by AD. Given the possible role for AQP1 in the progressive functional decline of CP in aging, and its hypothetical relationship to an increased risk of AD, AQP1 could be a potential drug target for novel therapy of AD.³⁷ Agonists of AQP1 could augment CSF production, enhancing the rate of CSF turnover.



Considering the above, it seems reasonable to speculate that pharmacological targeting of choroidal proteins essential for CSF production may provide a new therapeutic approach for Alzheimer's disease since such modulators may improve the CSF turnover and clearance of potentially toxic metabolites, such as β -amyloid, from the brain. Hence, choroidal proteins involved in CSF secretion may be promising pharmacological targets for Alzheimer's disease therapy.

Conclusions

Compromised function of the choroid plexus and defective CSF production and turnover, with diminished clearance of $A\beta$, may play an important role in late-onset forms of AD. If reduced CSF turnover is a risk factor for AD, then therapeutic strategies to improve CSF flow are reasonable. However, the role of deficient CSF dynamics in AD and the relevance of choroidal proteins as potential therapeutic targets to enhance CSF turnover have received relatively little research attention. In this paper, we discussed several choroidal proteins, such as Na^+-K^+ ATPase, carbonic anhydrase, and AQP1, that may be targets for pharmacological up-regulation of CSF formation. The search for potentially beneficial drugs useful to ameliorate AD by facilitating CSF production and turnover may be an important area for future research. However, the ultimate utility of such modulators in the management of AD remains to be determined. Here, we hypothesized that caffeine, the most commonly used psychoactive drug in the world, may be an attractive therapeutic candidate for treatment of AD since long-term caffeine consumption may augment CSF production. Other potential mechanisms of cognitive protection by caffeine have been suggested by recent studies.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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